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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,424	12/28/2000	Adrian Auf Der Maur	27656/37021	7858

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 02/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,424	DER MAUR ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,33-38 and 42-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,33-38 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/8/04 has been entered.

Status of Claims

Claims 31, 33-38 and 42-47 are pending and under examination.

Withdrawn Rejections

In view of the amendments to the claims and applicants' arguments the rejection under 35 USC 112 second paragraph is withdrawn. However, the newly amended claims are rejected as follows:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and

use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 33-38 and 42-47, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A). The as-filed specification does not provide support for the claim 31 amendment reciting "wherein the detection of the marker protein is not dependent upon the presence of an antigen for which the intrabody is specific".

Response to Arguments

Applicants state that these amendments are supported throughout the specification. But state that the presently added detection of marker protein is not antigen- dependent is not ipsis verbis within the specification. But that the written description is satisfied because one of ordinary skill in the art reviewing the disclosure would appreciate that applicants disclosed performing the claimed assays in a manner wherein

detection was not dependent on the antigen-antibody interaction. This is most clearly seen in Figures 1 and 2.

In reply, a review of Figures 1 and 2 from the Brief description of the Drawings do not convey with clarity the argued detection method. A further review of the specification (corresponds to US 2001/0024831), e.g., col. 5, paragraphs [0078-0081] state that "…….the principle of the quality control system as described in the present invention was demonstrated using a number of ***well characterised scFvs***. These possess essentially identical antigen binding properties but different ***in vitro stabilities***…..the intracellular stability and solubility of the Gal11P-Gal4AD-scFv fusion proteins depends on the scFv portion. Therefore, only stable and soluble scFv fusion proteins interacting sufficiently with LexA-Gal4(58-97) are able to ***activate reporter gene expression*** (e.g. .beta.-galactosidase) ……. A fusion of any single chain with the Gal11 wt allele is therefore unable to activate the reporter gene…neither the bait (LexA-Gal4(58-97)) nor the ***scFv fusion protein alone*** activate reporter gene expression…." (Emphasis added.)

A test of whether the claimed limitation is supported in the as-filed specification is not whether one skilled in the art would know that the disclosure performed the claimed assays.

Rather, whether the newly added limitation is present in the application as originally filed. Based on applicants' disclosure this appears not to be the case.

Applicants further argue that the claimed method is a screening method any unpredictability associated with the method is not inappropriate. While the results obtained by a screening method are by their very nature unpredictable (i.e., the methods screen unknowns for activity and one cannot predict the activity of a test sample before testing) the claimed method itself is reliable and no evidence has been presented that calls this reliability to question.

In response, applicants' attention is drawn to col. 1, Background Art discussion, specifically paragraph [0007]. Applicants acknowledge that it is still completely unpredictable whether an intrabody is functional within the cells, citing several arts therein. The reasons are most probably the different environments: phage display and other classical techniques are performed under oxidizing conditions, therefore disulfide bridges are formed, whereas intrabodies must function in reducing conditions. This reducing environment can lead to insufficient solubility of the intrabody and hence they form non-functional aggregates. It is further known in the art that rational

approaches such as modifying the VH and VL sequences of the intrabodies may lead to success in individual cases but may not be easily generally applied. Thus, as evident from the prior art and disclosure, nothing can be made general and each is tailored for each specific application. See further the rejection, infra.

Also the claimed "soluble and stable in ***selected conditions***" is not supported in the as-filed specification. The selected conditions would be broader in scope than the as-filed reducing conditions.

B). The specification does not provide an adequate written description of intrabodies that remain soluble and stable in a selected conditions by transformation of host cells with a nucleic acid library. There are no characterizing features for any of the components that ensure that a host transfected with any type of nucleic acid library still remains soluble and stable in a selected conditions. It is not apparent from the claims what conditions are selected to achieve such solubility and stability. The specification provides a general statement at to the claimed method. It is not apparent from the general statement the structure of a library attached to a marker protein that results inside a cell of a stable and soluble itnrabodies. As applicants state at page 8,paragrph 1 of the instant REMARKS, "….although

successful intrabodies were described, it was unpredictable whether any particular intrabody would be functional within a cell. This did not relate so much to the binding affinity of the scFv for the target antigen but rather to the stability and solubility of the intrabody in the intracellular environment, which was necessarily, different from that in which they were produced (e.g., phage display and other classical techniques were performed under oxidizing conditions while the intrabodies must function under reducing conditions.) Such a reducing environment can lead to insufficient solubility of the intrabody resulting in non-functional aggregates, despite selection in a phage display method. Accordingly, the value of mRNA derived libraries of different scFv fragments is limited in the identification of CDRS which have a high affinity for the antigen because the corresponding framework may be insoluble and tend to aggregate. Thus, in the absence of a detail description in the specification as to the components and methods necessary to achieve the object of the claimed, the specifics of the claimed method is not provided in the specification. A "written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials".

University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993)[The claims at issued in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)]. See also University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003).

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claim 36 which recites that identifying cells expressing a first and a second protein interacting with each other via a constant region of the first protein. The specification recites for a library for the constant region of the first protein. Cf. with the specification, page 34, line 31 up to page 19, line 18. Also, with the Examples.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 36-38 and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Visintin et al (PNAS) for reasons advanced in the last Office action.

Response to Arguments

Applicants argue that Visintin also relies upon the use of the two hybrid system for the isolation of intrabodies using an antibody/antigen interaction wherein the claimed identification of the intrabodies is based on the antigen dependent interaction between the antibody and its corresponding antigen. An examination of Figure 1 of Visintin et al. shows that the two-hybrid method was adapted "to detect antibody-antigen interaction in vivo." Thus, "If antibody-antigen interaction occurs, in vivo, the resulting complex can bind to the LexA DBS upstream of his or lacz genes" resulting in either growth of the transformed yeast or expression of a visible signal, respectively. Again, a comparison of Figure 1 of Visintin with Applicants' Figure 1 is solicited.

In reply, claim 36 also recites broadly an interaction between scfv(intrabody)i.e., a first protein comprising an intrabody with a transactivation system and a second protein comprising the second part of said transactivation system. This is the yeast two-hybrid method as taught by Visintin.

Claims 36-38 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Hoffler et al (US 20030017149).

Hoffler et al discloses at paragraph [0001] a method for screening DNA construct libraries for those which encode single-chain fragments of immunoglobulin variable domains (sFvs) (intrabodies, as claimed) having specificity for desired antigens in vivo using the activity of a transcriptional activator. At paragraph [0101], Hoffler discloses the fusion protein comprising at least one nuclear localization sequence (NLS). Hoffler at paragraph beginning at 0183] provides a detailed description of the method i.e., an example method for isolating single chain monoclonal antibody fusion reagents that target constitutive transcriptional activation peptide domains to endogenous signal-responsive transcriptional regulatory proteins wherein the CREB phosphorylation BOX peptide domain (CREB/P-BOX) is fused to the LexA DBD and acts as the LexA DBD/protein antigen X fusion of interest (the "bait") for screening immunoglobulin variable regions in this system. See FIG. 1. At paragraph [0184] Hoffler discloses, a single chain antibody fusion reagent molecule targets the CREB sequence in the antigen fusion, transcription factor function is reconstituted and the reporter genes (marker system, as claimed)

are activated allowing growth on selective media lacking histidine, as well as demonstrating beta-galactosidase activity. Positive interactions can be detected in this particular embodiment by selecting on plates lacking histidine, followed by a second screen for beta-galactosidase expression. Identification of the immunoglobulin fusion reagent (antibody/VP16 fusion, for example) which binds the LexA DBD/CREB/P-BOX antigen fusion is the ultimate goal of the screening protocol. Moreover, once isolated, the nucleic acid sequences which encode the immunoglobulin fusion reagent can be cloned into a mammalian expression vector and the targeting of CREB in the nucleus may be ascertained using reporter genes and endogenous genes that are known to harbor consensus camp responsive element (CRE) motifs.

Accordingly, the specific process steps of Hoeffler fully meet the broad claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable Visintin above in view of Ptashne et al (20040014036) for reasons of record.

Response to Arguments

Applicants argue that Ptashne too uses a two hybrid system relying upon a direct antibody-antigen interaction for the identification and isolation of intrabodies. Thus, Ptashne fails to provide any motivation to modify the systems disclosed by Visintin to provide the claimed invention.

In response, the arguments above under Visintin are applied herein. Ptashne is employed as providing the motivation to use GAL4 and GAL11P in the two yeast method of Visintin. Ptashne discloses at [0007]-[0008] that transcriptional activators activate transcription by a novel mechanism as they do not squelch known activators when they are over expressed in yeast. Without wishing to be bound by any particular theory, we propose that these activators function by interacting with a component of the RNA polymerase II holoenzyme; this hypothesis is consistent with the observation that the only other

transcriptional activator known not to squelch is Gall 1, which is part of the holoenzyme. The systems described herein utilize holoenzyme components, or factors that interact therewith, in a way that provides advantages over known transcriptional activation systems. For example, the protein-protein interaction systems that utilize Gal11 and/or Gal1P overcome some of difficulties known in the art with standard di-hybrid and interaction trap systems.

Claims 31, 33 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Visintin et al(PNAS).

Visintin discloses at pages 11726, col. 2 up to 11727, Fig. 5 a method by redox state of a scfv fusion protein in yeast cells by a gel mobility assay as shown in Fig. 5. The figure describes a scFvF8-VP16 expressed in the cytoplasm of yeast cells wherein secreted scFv fragment is expressed as a secreted protein in the endoplasmic reticulum of insect cells. Visintin discloses at page 11725, paragraph bridging col. 1 and col. 2 a panel of scFv derived further from mabs or from phage display antibody library, some of which had been shown to have biological activity when intracellularly expressed in vivo. (Note also page 11723, col. 1 wherein Visintin makes reference to Proba (J. Mol. Biol. as to the selection of intrabodies).

Accordingly, the claimed method is obvious over the disclosure or, at least suggestion, of an assay involving the redox state of fusion protein in yeast cell. It would have been obvious that this intermediate assay is done prior to the antigen-antibody reaction of the yeast hybrid system. It is well known in the art that prior to scfv-antigen reaction, the library has to be made and then tested for its property e.g., stability prior to identifying those that bind to a particular antigen. See the Proba reference cited by Visintin, above.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Visintin as applied to claims 31, 33, 35 above, and further in view of Martineau (J. Mol.Biol.) or Nolan et al (USP 6,153,380).

Visintin is discussed above. Visintin does not disclose a marker as the fluorescence activity. However, Martineau discloses at pages 923, col. 2 up to 925 the monitoring of the stability of scFv using its intrinsic fluorescence as a probe of the tertiary structure. Nolan discloses at col. 17, lines 5-16 the use of selectable markers which facilitates the selection of cells expressing peptides at uniformly high levels including self-fluorescent markers. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was used to use a marker having fluorescent activity

in the method of Visintin as taught by either Martineau or Nolan. The advantages taught by each of the references would motivate one having ordinary skill in the art to use said markers.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31, 33-38, 43-47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-23 and 39 of copending Application No. 10/169,179('179 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant broad claimed method of identifying scfv or intrabodies is obviously the method of the '179 application. The difference resides in

the '179 application mutations in the CDR contained in the scfv framework. It is considered that it is the CDR of the instant scfv framework that is similarly mutagenized, as shown in the instant and '179 specification that produce a library that identifies the scfv containing CDRs.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571)272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
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Tdw
February 21, 2005